# Osteoporosis: An Update on Screening, Diagnosis, Evaluation, and Treatment

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## abstract

Osteoporosis screening, diagnosis, and treatment have gained much attention in the health care community over the past 2 decades. During this time, creation of multispecialty awareness programs (eg, "Own the Bone," American Orthopedic Association; "Capture the Fracture," International Osteoporosis Foundation) and improvements in diagnostic protocols have been evident. Significant advances in technology have elucidated elements of genetic predisposition for decreased bone mineral density in the aging population. Additionally, several novel drug therapies have entered the market and provide more options for primary care and osteoporosis specialists to medically manage patients at risk for fragility fractures. Despite this, adherence to osteoporosis screening and treatment protocols has been surprisingly low by health care practitioners, including orthopedic surgeons. Continued awareness and education of this skeletal disorder is crucial to effectively care for our aging population. [*Orthopedics*. 2023;46(1):e20-e26.]


Over a person's lifespan, bone is acquired during growth, reaches peak bone mineral density (BMD) in early adulthood, and is lost with advancing age. Osteoporosis is defined as a low BMD with deterioration in the microarchitectural structure of bone tissue resulting in skeletal fragility and increased risk of fracture.[1,2] Previous studies estimated a 10.3% prevalence of osteoporosis in the United States among individuals 50 years and older.[3] In 2017, Wright et al[4] demonstrated that approximately 16.9% of men and 29.9% of women 50 years and older meet the updated diagnostic criteria for osteoporosis as defined by the National Bone Health Alliance. This prevalence increases to 46.3% in men and 77.1% in women 80 years and older.

The most obvious clinical sign of osteoporosis is a fragility fracture. When considering fracture risk, Kanis et al[5] estimated a lifetime risk of developing a major osteoporotic fracture (spine, hip, forearm, humerus) at 46.4% for women and 22.4% for men. In 2000, the worldwide incidence of fragility fractures was estimated to be 9.0 million, and projections show a total of 3 million fragility fractures in the United States alone by 2025.[6,7] Osteoporotic fractures have been shown to account for loss of more disability-adjusted life years than most common cancers, and a fragility hip fracture has an almost 30% 1-year mortality rate.[6,8] This underscores the importance of recognizing and treating osteoporosis as well as advancing our understanding of the disease to develop newer therapeutics with fewer side effects.

### Osteoporosis and Genetics

While fracture is the clinical event of most importance in osteoporosis, this phenotype can be challenging to study ge-

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netically.[9] Parental osteoporotic fracture is predictive of future risk of fracture in their children, highlighting the existence of a genetic contribution to this disease. There are a large number of rare monogenic diseases that can affect bone mass and strength, but these disease alleles contribute very little to the variation observed in BMD in the population as a whole.[10,11] Rather, BMD is a complex trait with multiple alleles dictating the genetic proportion of peak BMD in any one person.[12] The proportion of heritable genetic influence on peak BMD has been estimated to be as high as 85%, and equally high heritabilities have been noted for bone architectural phenotypes that are predictive of fracture.[13-16]

Historically, linkage analysis and candidate gene testing were used to find associations between regions of the genome and a phenotype of interest, but these have not been successful in finding the actual genes associated with BMD.[17,18] There are many types of genetic changes that can cause differences in phenotype and/or lead to disease. While mutations can involve multiple base pairs, such as is seen with genomic duplications and deletions, mutations may be as a small as a single base pair (SNP). Genome-wide association studies (GWAS) are now much more frequently used for genetic mapping. In short, a GWAS is an approach by which the whole genome is examined for associations between genotype and phenotype (reviewed by Uitterlinden[18]). A population ranging in size from a few hundred to several thousand persons is phenotyped for a trait of interest. Then arrays are used to find associations between phenotypes of interest and SNP variants. Across the human population, approximately 10 million SNPs have been found, and on average there is an SNP every 300 base pairs.[19] Genetic variants may alter the amino acid composition and potentially the function of a protein product of a gene.[9] However, in complexly inherited diseases such as osteoporosis, the causative variant is often located outside of the protein coding region of the gene and may affect the expression of a single gene or multiple genes in a region.[20]

## What Has GWAS Taught Us About Osteoporosis?

The first GWAS for BMD was conducted on data from approximately 1000 individuals from the Framingham Osteoporosis Study and established the principle that BMD could be investigated using GWAS.[21] In 2009, Rivadeneira et al[22] identified 20 GWAS loci for BMD that met the accepted significance cutoff. In the intervening decade, a large number of GWAS studies have been conducted in adults, yielding loci associated with BMD of the total hip, forearm, spine, and more recently for whole-body BMD sans the head (reviewed by Trajanoska and Rivadeneira[23]). A recent meta-analysis of GWAS for whole-body BMD showed that when the data were stratified by age, only 2 of the 80 identified loci were affected by age. This means that the majority of genetic loci exert their effects by affecting peak BMD and that the consequences of these loci on peak BMD persist over the life of the individual. In essence, osteoporosis is a young person's disease wherein there is a failure to acquire adequate peak BMD, predisposing a person for fragility fracture in later life.

Osteoporosis is an exceedingly complex common disease. Historically, GWAS was conducted under the common variant hypothesis, which roughly stated that common disease was caused by common variants.[18] The newest studies include rare variants in the analysis and show that the effect size of rare variants is often larger than that of common variants, but this explains only approximately 20% of the population variance in BMD.[12] Likely, some of this can be ascribed to gene by environment (G*E) and gene by gene (G*G) interactions that could not be accounted for in study design.[18] An interpretation of these results is that "osteoporosis" is actually a collection of syndromes, but it is unknown at this time if parsing out the "kind" of osteoporosis a person has would be of clinical value.

There has been much interest in using these results to calculate risk scores to identify patients at high risk for developing disease.[24] In principle, these risk scores are not that different from risk assessment tools already available, such as the commonly used Fracture Risk Assessment Tool (FRAX).[25] A polygenic risk score totals how many disease-associated variants a person has, weighs each variant based on how much of an effect that variant has on the phenotype, and yields a mathematical calculation of the risk of developing a disease based on their genotypes.[24] There have been mixed results to date in the creation of polygenic risk scores for osteoporosis, but this is a quickly evolving and promising area of research.[26] A hope for this technology is that these scores can be used to determine who might benefit most from costly medications that are not without serious side effects, such as romosozumab, which is effective in preventing fracture but is associated with increased risk for stroke and heart attacks.[26]

## Diagnosis of Osteoporosis

The diagnosis of osteoporosis is made when patients meet any of the following criteria[27,28]:

1. Fragility fracture
2. T-score ≤ -2.5 at the lumbar spine, femoral neck, total hip, or distal one-third of the radius on dual-energy x-ray absorptiometry (DXA) examination
3. T-score between -1.0 and -2.5 with elevated fracture risk as determined by country-specific thresholds using the online FRAX.[29] In the United States, the cutoffs for 10-year fracture risk estimates are ≥20% risk of major osteoporotic fracture and ≥3% risk of hip fracture.

The lowest T-score on an individual's DXA examination is used for diagnosis. For example, a postmenopausal 65-year-old woman with a T-score of -2.6 at the lumbar spine and -2.0 at the left femoral neck and left total hip meets criteria for

osteoporosis and should not be classified as having osteoporosis at the spine and osteopenia at the hip. The National Osteoporosis Foundation recommends screening DXA to assess BMD at the lumbar spine and one or both hips (±distal radius under certain clinical circumstances such as primary hyperparathyroidism) in the following groups[27]: women 65 years and older; men 70 years and older; and postmenopausal women and men 50 years and older with risk factors for osteoporosis (eg, premature menopause, rheumatoid arthritis, use of bone harming medications) and those with a history of adult fracture.

## Clinical Evaluation of Osteoporosis and Secondary Causes of Osteoporosis

Primary osteoporosis is osteoporosis due to aging and/or postmenopausal status. An individual suspected of having osteoporosis, either due to fragility fracture and/or low BMD by DXA, should have an evaluation to rule out secondary causes (**Table A**).[30-35] A DXA machine cannot distinguish the difference between low BMD due to osteoporosis or low BMD due to osteomalacia. Therefore, the clinician should perform an appropriate evaluation and associated laboratory studies. Secondary causes are found in approximately 30% of postmenopausal women and 50% to 80% of men,[32,33] often in those with very low Z-scores.[30] **Table A** provides a list of common causes of secondary osteoporosis.

Evaluation for secondary causes of osteoporosis consists of a thorough history and physical examination and preliminary laboratory evaluation. The history and physical examination should be targeted at fracture history (particularly number, site, trauma vs atraumatic, age of onset) and predisposing factors for low BMD, including genetic (family history) or environmental exposures (tobacco use, excess alcohol/caffeine intake, exposure to steroids or other bone-harming medications, malabsorption, or inadequate intake). For women, age at menarche and menstrual, obstetric, and menopausal histories, including use of hormones, should be sought. It may also be important to determine if low BMD is due to low peak BMD or ongoing bone loss. For most orthopedic surgeons, this goes beyond the typical scope of practice; therefore, we recommend referral to either a patient's primary care provider or an endocrinologist. With that being said, these physicians often have a significant wait time for evaluation, and all physicians should be able to initiate the initial workup for osteoporosis.

**Table B** contains a suggested laboratory evaluation to rule out secondary causes of osteoporosis in otherwise healthy individuals. The suggested panel should identify greater than 90% of secondary causes of osteoporosis, if present.[32,36] In particular, osteomalacia due to inadequate calcium (often due to vitamin D deficiency) or phosphorous must be ruled out or treated prior to initiating pharmacotherapy to avoid increased risk of side effects (eg, hypocalcemia with antiresorptive medications). Additional laboratory evaluation (serum and urine protein electrophoresis, celiac panel, magnesium, serum tryptase, 1-mg dexamethasone suppression test, 1,25-dihydroxyvitamin D, bone turnover markers) should be performed as guided by history and physical examination findings and comorbidities. If height loss is reported or observed, imaging of the thoracic and lumbar spine should be performed to rule out vertebral compression fractures (**Table C**). Recent chest radiographs and/or abdominal imaging can be used to evaluate the spine without additional cost or radiation exposure.

## Updates in Osteoporosis Treatment

Once osteoporosis has been confirmed and any underlying abnormalities have been corrected (eg, vitamin D deficiency, primary hyperparathyroidism), treatment should be considered in those individuals meeting appropriate criteria[30,31,37,38] (**Table D**). Diagnosis and treatment of osteoporosis has decreased over recent decades in part due to lack of recognition that fragility fractures are diagnostic of osteoporosis and fear of medication side effects.[39] Orthopedists are often the first providers involved in patient care when a fracture occurs and, therefore, are uniquely positioned to inform the patient who experienced a fragility fracture that they have osteoporosis and should have appropriate osteoporosis evaluation and treatment. Fracture liaison services (discussed hereafter) can assist orthopedists with the evaluation and treatment of osteoporosis when patients present with fracture. Importantly, osteoporosis therapy consists of pharmacologic and non-pharmacologic treatments.

Non-pharmacological therapy includes adequate calcium/vitamin D/protein intake, smoking cessation, fall prevention, avoiding bone-harming medications (if possible), maintaining a healthy weight, remaining active with weight-bearing exercise, and avoiding excess alcohol and caffeine intake. The Institute of Medicine[40] and National Osteoporosis Foundation[31] recommend individuals older than 50 years target 1000 to 1200 mg of calcium per day, including and preferably via dietary intake.[37,38] If a supplement is needed to make up the difference in those unable to get the recommended amount exclusively via diet, calcium carbonate (40% elemental calcium, must be taken with food) or calcium citrate (21% elemental calcium, more expensive, can be taken with or without food, better absorbed in achlorhydria such as proton pump inhibitor use or gastric bypass) may be used. The Institute of Medicine[40] recommends 400 to 600 IU/d of vitamin D for healthy adults 51 years and older, whereas most osteoporosis guidelines recommend 800 to 2000 IU/d to achieve adequate 25-hydroxyvitamin D levels.[30,31,37,38] The appropriate vitamin D level is a matter of debate.[40,41] Our practice is in line with the Endocrine Society Guidelines targeting a 25-hydroxyvitamin D level of 30 ng/

mL.[30,41] Vitamin D3 (aka cholecalciferol) is preferred to vitamin D2 due to its longer half-life.[42] Calcium and vitamin D are "threshold" vitamins, meaning that adequate amounts are important for mineralization, maintaining BMD, and avoiding excess BMD loss, but more (and particularly excessive amounts) are not necessarily better.

Osteoporosis pharmacotherapy is classically divided into 2 categories: antiresorptive or anabolic. Societal guidelines are available that provide suggested treatment algorithms to help medical providers select the appropriate pharmacotherapy for their patients.[28,37,38] Antiresorptive therapies (bisphosphonates, denosumab, raloxifene) target and block osteoclast activity to decrease bone resorption and BMD loss. All antiresorptive therapies can cause hypocalcemia and are associated with osteonecrosis of the jaw and atypical femur fracture, which occur in less than 1% of patients.[43-45] Anabolic therapies (eg, teriparatide, abaloparatide) transiently stimulate the parathyroid hormone receptor to stimulate osteoblasts and bone formation. The most recently Food and Drug Administration–approved osteoporosis medication, romosozumab, is a monoclonal antibody to sclerostin and therefore has both antiresorptive and anabolic features. By inhibiting sclerostin (an inhibitor of bone formation), romosozumab stimulates bone formation and suppresses bone resorption.[46] In the FRAME study,[47] romosozumab for 12 months followed by 12 months of denosumab significantly decreased the risk of vertebral compression fractures in postmenopausal women with osteoporosis compared with placebo for 12 months followed by 12 months of denosumab (risk ratio, 0.25; $P<.001$). Although romosozumab resulted in significantly greater increases in BMD at the lumbar spine, total hip, and femoral neck, nonvertebral and hip fractures were not statistically significantly different between the romosozumab and placebo groups. Similar to other antiresorptive medications, osteonecrosis of the jaw and atypical femur fractures have been reportedly rarely with romosozoumab.[47] Uniquely, romosozumab carries a black box warning for potentially increased risk of myocardial infarction, stroke, and cardiovascular death and should not be initiated in those who have had a cardiovascular event within the previous 12 months. Romosozumab is a subcutaneous injection administered in a health care facility monthly and is only approved for 12 months of use. **Table E** lists pharmacological treatment options for osteoporosis.[48-60]

## Assessment of Osteoporosis Management

Despite the increasing prevalence of osteoporosis and expected increase in fragility fracture rate, there appears to be an overall poor adherence to osteoporosis screening and treatment protocols. Studies have found that less than 25% of patients for whom osteoporosis screening is recommended receive such screening.[61] A 2019 study demonstrated that in patients 50 years and older who presented to the emergency department with a vertebral fragility fracture, only 27% were receiving medical therapy for osteoporosis prior to their fracture.[7] As our knowledge of screening guidelines and adherence to their recommendations certainly lacks, so does our post-fragility fracture care of bone health. Studies demonstrate an almost 200% increased risk of subsequent fragility fracture and an almost 300% increased risk of hip fracture following a vertebral fragility fracture.[62] In 2016, Oertel et al[63] evaluated osteoporosis management in 1375 geriatric patients following fragility fractures and found that only 21% of patients were previously tested for BMD or received osteoporosis treatment. Similarly, another study found that 1 year after fragility fracture, more than 90% of patients failed to receive a bone density scan or start empiric treatment for osteoporosis.[7] Ultimately, 38% of patients in this study went on to develop a second osteoporotic fracture within 2 years of their initial fragility fracture.[7] These results highlight the fact that we are slow to diagnose and treat osteoporosis before fragility fractures occur. Even more concerning, they demonstrate a generalized lack of understanding about the need for testing and treatment following fragility fractures to prevent future fractures.

Beyond the lack of understanding about the need for testing and treatment for osteoporosis, there are also significant patient factors to consider, especially noncompliance. While there are a variety of reasons for poor patient compliance, it has previously been shown that patient adherence to treatment correlates with decreased fragility fracture risk as well as improvement in BMD.[64] Therefore, it is incredibly important to discuss areas of patient concern, including their understanding of the diagnosis and treatment plan, as well as the potential consequences of untreated osteoporosis as well as the side effects of medications. While clinicians believe more than 67% of their patients are taking their prescribed osteoporosis medications, only 40% of patients are picking up the medications, and it is likely that even fewer are actually taking the medications as prescribed.[65] From a patient standpoint, the major reasons for noncompliance include side effect profile of the medications, lack of education/awareness of benefits of treatment, and dosing/administration inconveniences.[65] It is our recommendation that practitioners treating osteoporosis have in-depth discussions with their patients regarding the side effect profiles of the medications they prescribe. They should also stress the significant morbidity/mortality associated with untreated osteoporosis and the benefits of treatment.

## Areas of Improvement

Initially implemented in the United Kingdom, a fracture liaison service (FLS) is a coordinator-based, post-fracture model

of care designed to close the gap between sentinel fragility fracture and secondary fracture.[66] The aim is to create a structured pathway to improve identification, evaluation, and implementation of appropriate treatment in patients at risk of a secondary fragility fracture. A successful FLS program generally consists of a core of 3 individuals: physician leader, FLS coordinator, and nurse navigator. Outside the core, significant multispecialty assistance is necessary and includes orthopedic surgery, rheumatology, endocrinology, primary care, and nursing support.[67] The International Osteoporosis Foundation launched their "Capture the Fracture" program in 2012 and provided guidance on development of FLS programs globally.[68] When comparing institutions with FLS programs in place vs non-FLS institutions, an approximate 30% reduction in any refracture and a 40% reduction in major refractures have been reported.[69] Gupta et al[70] described their institution's unique FLS program supplemented with electronic medical record–based alerts. These alerts helped identify at-risk patients who were admitted to the hospital or evaluated in the emergency department. After implementation for 12 months, the authors[70] reported their ability to identify "captured missed opportunities" in 73.1% of previously undiagnosed and 77.1% of previously untreated osteoporosis patients. Although success of FLS may vary, key factors that influence effectiveness include multidisciplinary involvement, dedicated case managers, regular assessment and follow-up, multifaceted interventions, and patient education.[71] The authors of this article recommend that an FLS be developed at each institution to improve diagnosis and treatment of individuals with osteoporosis.

## Conclusion

In 2004, the US Surgeon General report warned that, in 2020, the prevalence of osteoporosis and low bone mass was expected to increase to 1 in 2 Americans older than 50 years. While data for 2020 are pending, results from 2017–2018 demonstrate that low bone mass at the femoral neck and/or the lumbar spine was present in 51.5% of females and 33.5% of males 50 years or older.[72] We have made significant progress in understanding the genetic etiology of osteoporosis and development of treatments.[73] As our understanding of this diseased has improved, a greater number of pharmacotherapy options have become available for treatment.

While we continue to make great strides in the understanding of the disease and development of treatment modalities, there is continued need for improvement in screening and implementation of treatment. Many age-appropriate patients do not receive screening or counseling on osteoporosis. Furthermore, patients with known fragility fractures do not consistently receive the osteoporosis care and treatment they most certainly need. With more than 53 million people in the United States alone affected by this disease, a thorough understanding of the basis, screening, diagnosis, and treatment of osteoporosis is vital for all practitioners.

## References


1. Bunta AD. It is time for everyone to own the bone. *Osteoporos Int*. 2011;22(3)(suppl 3):477-482. https://doi.org/10.1007/s00198-011-1704-0 PMID:21847769
2. Ensrud KE, Crandall CJ. Osteoporosis. *Ann Intern Med*. 2017;167(3):ITC17-ITC32. https://doi.org/10.7326/AITC201708010 PMID:28761958
3. Wright NC, Looker AC, Saag KG, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res*. 2014; 29(11):2520-2526. https://doi.org/10.1002/jbmr.2269 PMID:24771492
4. Wright NC, Saag KG, Dawson-Hughes B, Khosla S, Siris ES. The impact of the new National Bone Health Alliance (NBHA) diagnostic criteria on the prevalence of osteoporosis in the USA. *Osteoporos Int*. 2017;28(4):1225-1232. https://doi.org/10.1007/s00198-016-3865-3 PMID:27966104
5. Kanis JA, Johnell O, Oden A, et al. Long-term risk of osteoporotic fracture in Malmö. *Osteoporos Int*. 2000;11(8):669-674. https://doi.org/10.1007/s001980070064 PMID:11095169
6. Johnell O, Kanis JA. An estimate of the worldwide prevalence and disability associated with osteoporotic fractures. *Osteoporos Int*. 2006;17(12):1726-1733. https://doi.org/10.1007/s00198-006-0172-4 PMID:16983459
7. Barton DW, Behrend CJ, Carmouche JJ. Rates of osteoporosis screening and treatment following vertebral fracture. *Spine J*. 2019;19(3):411-417. https://doi.org/10.1016/j.spinee.2018.08.004 PMID:30142455
8. Kannegaard PN, van der Mark S, Eiken P, Abrahamsen B. Excess mortality in men compared with women following a hip fracture: national analysis of comedications, comorbidity and survival. *Age Ageing*. 2010;39(2):203-209. https://doi.org/10.1093/ageing/afp221 PMID:20075035
9. Koromani F, Trajanoska K, Rivadeneira F, Oei L. Recent advances in the genetics of fractures in osteoporosis. *Front Endocrinol (Lausanne)*. 2019;10:337. https://doi.org/10.3389/fendo.2019.00337 PMID:31231309
10. Hannan FM, Newey PJ, Whyte MP, Thakker RV. Genetic approaches to metabolic bone diseases. *Br J Clin Pharmacol*. 2019;85(6):1147-1160. https://doi.org/10.1111/bcp.13803 PMID:30357886
11. Yuan J, Tickner J, Mullin BH, et al. Advanced genetic approaches in discovery and characterization of genes involved with osteoporosis in mouse and human. *Front Genet*. 2019;10:288. https://doi.org/10.3389/fgene.2019.00288 PMID:31001327
12. Morris JA, Kemp JP, Youlten SE, et al; 23andMe Research Team. An atlas of genetic influences on osteoporosis in humans and mice. *Nat Genet*. 2019;51(2):258-266. https://doi.org/10.1038/s41588-018-0302-x PMID:30598549
13. Hernandez-de Sosa N, Athanasiadis G, Malouf J, et al. Genetic contribution of femoral neck bone geometry to the risk of developing osteoporosis: a family-based study. *PLoS One*. 2016;11(5):e0154833. https://doi.org/10.1371/journal.pone.0154833 PMID:27163365
14. Hsu YH, Estrada K, Evangelou E, et al. Meta-analysis of genomewide association studies reveals genetic variants for hip bone geometry. *J Bone Miner Res*. 2019;34(7):1284-1296. https://doi.org/10.1002/jbmr.3698 PMID:30888730
15. Karasik D, Demissie S, Zhou Y, et al. Heritability and genetic correlations for bone microarchitecture: the Framingham Study families. *J Bone Miner Res*. 2017;32(1):106-114. https://doi.org/10.1002/jbmr.2915 PMID:27419666
16. Ralston SH, Uitterlinden AG. Genetics of osteoporosis. *Endocr Rev*. 2010;31(5):629-662. https://doi.org/10.1210/er.2009-0044 PMID:20431112
17. Richards JB, Kavvoura FK, Rivadeneira F, et al; Genetic Factors for Osteoporosis

Consortium. Collaborative meta-analysis: associations of 150 candidate genes with osteoporosis and osteoporotic fracture. *Ann Intern Med*. 2009;151(8):528-537. https://doi.org/10.7326/0003-4819-151-8-200910200-00006 PMID:19841454

18. Uitterlinden A. An introduction to genome-wide association studies: GWAS for dummies. In: *Seminars in Reproductive Medicine*. Thieme Medical Publishers; 2016. https://doi.org/10.1055/s-0036-1585406
19. Pratt CW, Gill KJ, Barrett NM, Roberts MM. Symptoms and etiology of serious mental illness. In: Pratt CW, Gill KJ, Barrett NM, Roberts MM, eds. *Psychiatric Rehabilitation*, 3rd ed. Academic Press; 2014:33-74. https://doi.org/10.1016/B978-0-12-387002-5.00002-0
20. Chesi A, Wagley Y, Johnson ME, et al. Genome-scale Capture C promoter interactions implicate effector genes at GWAS loci for bone mineral density. *Nat Commun*. 2019;10(1):1260. https://doi.org/10.1038/s41467-019-09302-x PMID:30890710
21. Kiel DP, Demissie S, Dupuis J, Lunetta KL, Murabito JM, Karasik D. Genome-wide association with bone mass and geometry in the Framingham Heart Study. *BMC Med Genet*. 2007;8(suppl 1):S14. https://doi.org/10.1186/1471-2350-8-S1-S14 PMID:17903296
22. Rivadeneira F, Styrkársdottir U, Estrada K, et al; Genetic Factors for Osteoporosis (GEFOS) Consortium. Twenty bone-mineral-density loci identified by large-scale meta-analysis of genome-wide association studies. *Nat Genet*. 2009;41(11):1199-1206. https://doi.org/10.1038/ng.446 PMID:19801982
23. Trajanoska K, Rivadeneira F. The genetic architecture of osteoporosis and fracture risk. *Bone*. 2019;126:2-10. https://doi.org/10.1016/j.bone.2019.04.005 PMID:30980960
24. Sugrue LP, Desikan RS. What are polygenic scores and why are they important? *JAMA*. 2019;321(18):1820-1821. https://doi.org/10.1001/jama.2019.3893 PMID:30958510
25. Kanis JA, Johansson H, Harvey NC, McCloskey EV. A brief history of FRAX. *Arch Osteoporos*. 2018;13(1):118. https://doi.org/10.1007/s11657-018-0510-0 PMID:30382424
26. Gibson G. On the utilization of polygenic risk scores for therapeutic targeting. *PLoS Genet*. 2019;15(4):e1008060. https://doi.org/10.1371/journal.pgen.1008060 PMID:31022172
27. Cosman F, de Beur SJ, LeBoff MS, et al; National Osteoporosis Foundation. Clinician's guide to prevention and treatment of osteoporosis. *Osteoporos Int*. 2014;25(10):2359-2381. https://doi.org/10.1007/s00198-014-2794-2 PMID:25182228
28. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists/American College of Endocrinology clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis: 2020 update. *Endocr Pract*. 2020;26(suppl 1):1-46. https://doi.org/10.4158/GL-2020-0524SUPPL PMID:32427503
29. Kanis JA, Harvey NC, Cooper C, Johansson H, Odén A, McCloskey EV; Advisory Board of the National Osteoporosis Guideline Group. A systematic review of intervention thresholds based on FRAX: a report prepared for the National Osteoporosis Guideline Group and the International Osteoporosis Foundation. *Arch Osteoporos*. 2016;11(1):25. doi: 10.1007/s11657-016-0278-z. PMID: 27465509
30. Camacho PM, Petak SM, Binkley N, et al. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical Practice Guidelines for the Diagnosis and Treatment of Postmenopausal Osteoporosis 2016: Executive summary. *Endocr Pract*. 2016;22(9):1111-1118. https://doi.org/10.4158/EP161435.ESGL PMID:27643923
31. Weaver CM, Gordon CM, Janz KF, et al. The National Osteoporosis Foundation's position statement on peak bone mass development and lifestyle factors: a systematic review and implementation recommendations. *Osteoporos Int*. 2016:27:1281-1386. https://doi.org/10.1007/s00198-015-3440-3
32. Diab DL, Watts NB. Secondary osteoporosis: differential diagnosis and workup. *Clin Obstet Gynecol*. 2013;56(4):686-693. https://doi.org/10.1097/GRF.0b013e3182a9b5f9 PMID:24100597
33. Mirza F, Canalis E. Management of endocrine disease. Secondary osteoporosis: pathophysiology and management. *Eur J Endocrinol*. 2015;173(3):R131-R151. https://doi.org/10.1530/EJE-15-0118 PMID:25971649
34. Emkey GR, Epstein S. Secondary osteoporosis: pathophysiology & diagnosis. *Best Pract Res Clin Endocrinol Metab*. 2014;28(6):911-935. https://doi.org/10.1016/j.beem.2014.07.002 PMID:25432361
35. Crandall C. Laboratory workup for osteoporosis: which tests are most cost-effective? *Postgrad Med*. 2003;114(3):35-38, 41-44. https://doi.org/10.3810/pgm.2003.09.1492 PMID:14503399
36. Tannenbaum C, Clark J, Schwartzman K, et al. Yield of laboratory testing to identify secondary contributors to osteoporosis in otherwise healthy women. *J Clin Endocrinol Metab*. 2002;87(10):4431-4437. https://doi.org/10.1210/jc.2002-020275 PMID:12364413
37. Eastell R, Rosen CJ, Black DM, Cheung AM, Murad MH, Shoback D. Pharmacological management of osteoporosis in postmenopausal women: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2019;104(5):1595-1622. https://doi.org/10.1210/jc.2019-00221 PMID:30907953
38. Shoback D, Rosen CJ, Black DM, Cheung AM, Murad MH, Eastell R. Pharmacological management of osteoporosis in postmenopausal women: an endocrine society guideline update. *J Clin Endocrinol Metab*. 2020;105(3):587-594. https://doi.org/10.1210/clinem/dgaa048 PMID:32068863
39. Compston J. Reducing the treatment gap in osteoporosis. *Lancet Diabetes Endocrinol*. 2020;8(1):7-9. https://doi.org/10.1016/S2213-8587(19)30378-X PMID:31757770
40. Institute of Medicine. *Dietary Reference Intakes for Calcium and Vitamin D*. The National Academies Press; 2011.
41. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2011;96(7):1911-1930. https://doi.org/10.1210/jc.2011-0385 PMID:21646368
42. Romagnoli E, Mascia ML, Cipriani C, et al. Short and long-term variations in serum calciotropic hormones after a single very large dose of ergocalciferol (vitamin D2) or cholecalciferol (vitamin D3) in the elderly. *J Clin Endocrinol Metab*. 2008;93(8):3015-3020. https://doi.org/10.1210/jc.2008-0350 PMID:18492750
43. Sellmeyer DE. Atypical fractures as a potential complication of long-term bisphosphonate therapy. *JAMA*. 2010;304(13):1480-1484. https://doi.org/10.1001/jama.2010.1360 PMID:20924014
44. Khan AA, Morrison A, Hanley DA, et al; International Task Force on Osteonecrosis of the Jaw. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. *J Bone Miner Res*. 2015;30(1):3-23. https://doi.org/10.1002/jbmr.2405 PMID:25414052
45. Shane E, Burr D, Abrahamsen B, et al. Atypical subtrochanteric and diaphyseal femoral fractures: second report of a task force of the American Society for Bone and Mineral Research. *J Bone Miner Res*. 2014;29(1):1-23. https://doi.org/10.1002/jbmr.1998 PMID:23712442
46. McClung MR, Grauer A, Boonen S, et al. Romosozumab in postmenopausal women with low bone mineral density. *N Engl J Med*. 2014;370(5):412-420. https://doi.org/10.1056/NEJMoa1305224 PMID:24382002
47. Cosman F, Crittenden DB, Adachi JD, et al. Romosozumab treatment in postmenopausal women with osteoporosis. *N Engl J Med*. 2016;375(16):1532-1543. https://doi.org/10.1056/NEJMoa1607948 PMID:27641143
48. Liberman UA, Weiss SR, Bröll J, et al; The Alendronate Phase III Osteoporosis Treatment Study Group. Effect of oral alendronate on bone mineral density and the incidence of fractures in postmenopausal osteoporosis. *N Engl J Med*. 1995;333(22):1437-1443. https://

doi.org/10.1056/NEJM199511303332201 PMID:7477143

49. Black DM, Schwartz AV, Ensrud KE, et al; FLEX Research Group. Effects of continuing or stopping alendronate after 5 years of treatment: the Fracture Intervention Trial Long-term Extension (FLEX): a randomized trial. *JAMA*. 2006;296(24):2927-2938. https://doi.org/10.1001/jama.296.24.2927 PMID:17190893
50. Papapoulos SE, Quandt SA, Liberman UA, Hochberg MC, Thompson DE. Meta-analysis of the efficacy of alendronate for the prevention of hip fractures in postmenopausal women. *Osteoporos Int*. 2005;16(5):468-474. https://doi.org/10.1007/s00198-004-1725-z PMID:15448985
51. Cranney A, Wells G, Willan A, et al; Osteoporosis Methodology Group and The Osteoporosis Research Advisory Group. Meta-analyses of therapies for postmenopausal osteoporosis: II. Meta-analysis of alendronate for the treatment of postmenopausal women. *Endocr Rev*. 2002;23(4):508-516. https://doi.org/10.1210/er.2001-2002 PMID:12202465
52. Harris ST, Watts NB, Genant HK, et al; Vertebral Efficacy With Risedronate Therapy (VERT) Study Group. Effects of risedronate treatment on vertebral and nonvertebral fractures in women with postmenopausal osteoporosis: a randomized controlled trial. *JAMA*. 1999;282(14):1344-1352. https://doi.org/10.1001/jama.282.14.1344 PMID:10527181
53. McClung MR, Geusens P, Miller PD, et al; Hip Intervention Program Study Group. Effect of risedronate on the risk of hip fracture in elderly women. *N Engl J Med*. 2001;344(5):333-340. https://doi.org/10.1056/NEJM200102013440503 PMID:11172164
54. Chesnut CH III, Skag A, Christiansen C, et al; Oral Ibandronate Osteoporosis Vertebral Fracture Trial in North America and Europe (BONE). Effects of oral ibandronate administered daily or intermittently on fracture risk in postmenopausal osteoporosis. *J Bone Miner Res*. 2004;19(8):1241-1249. https://doi.org/10.1359/JBMR.040325 PMID:15231010
55. Black DM, Delmas PD, Eastell R, et al; HORIZON Pivotal Fracture Trial. Once-yearly zoledronic acid for treatment of postmenopausal osteoporosis. *N Engl J Med*. 2007;356(18):1809-1822. https://doi.org/10.1056/NEJMoa067312 PMID:17476007
56. Ettinger B, Black DM, Mitlak BH, et al; Multiple Outcomes of Raloxifene Evaluation (MORE) Investigators. Reduction of vertebral fracture risk in postmenopausal women with osteoporosis treated with raloxifene: results from a 3-year randomized clinical trial. *JAMA*. 1999;282(7):637-645. https://doi.org/10.1001/jama.282.7.637 PMID:10517716
57. Cummings SR, San Martin J, McClung MR, et al; FREEDOM Trial. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. *N Engl J Med*. 2009;361(8):756-765. https://doi.org/10.1056/NEJMoa0809493 PMID:19671655
58. Anastasilakis AD, Polyzos SA, Makras P, Aubry-Rozier B, Kaouri S, Lamy O. Clinical features of 24 patients with rebound-associated vertebral fractures after denosumab discontinuation: systematic review and additional cases. *J Bone Miner Res*. 2017;32(6):1291-1296. https://doi.org/10.1002/jbmr.3110 PMID:28240371
59. Neer RM, Arnaud CD, Zanchetta JR, et al. Effect of parathyroid hormone (1-34) on fractures and bone mineral density in postmenopausal women with osteoporosis. *N Engl J Med*. 2001;344(19):1434-1441. https://doi.org/10.1056/NEJM200105103441904 PMID:11346808
60. Miller PD, Hattersley G, Riis BJ, et al; ACTIVE Study Investigators. Effect of abaloparatide vs placebo on new vertebral fractures in postmenopausal women with osteoporosis: a randomized clinical trial. *JAMA*. 2016;316(7):722-733. https://doi.org/10.1001/jama.2016.11136 PMID:27533157
61. Gillespie CW, Morin PE. Trends and disparities in osteoporosis screening among women in the United States, 2008-2014. *Am J Med*. 2017;130(3):306-316. https://doi.org/10.1016/j.amjmed.2016.10.018 PMID:27884649
62. Black DM, Arden NK, Palermo L, Pearson J, Cummings SR; Study of Osteoporotic Fractures Research Group. Prevalent vertebral deformities predict hip fractures and new vertebral deformities but not wrist fractures. *J Bone Miner Res*. 1999;14(5):821-828. https://doi.org/10.1359/jbmr.1999.14.5.821 PMID:10320531
63. Oertel MJ, Graves L, Al-Hihi E, et al. Osteoporosis management in older patients who experienced a fracture. *Clin Interv Aging*. 2016;11:1111-1116. https://doi.org/10.2147/CIA.S107720 PMID:27578967
64. Siris ES, Selby PL, Saag KG, Borgström F, Herings RM, Silverman SL. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. *Am J Med*. 2009;122(2)(suppl):S3-S13. https://doi.org/10.1016/j.amjmed.2008.12.002 PMID:19187810
65. Curtis JR, Cai Q, Wade SW, et al. Osteoporosis medication adherence: physician perceptions vs. patients' utilization. *Bone*. 2013;55(1):1-6. https://doi.org/10.1016/j.bone.2013.03.003 PMID:23502042
66. McLellan AR, Gallacher SJ, Fraser M, McQuillian C. The fracture liaison service: success of a program for the evaluation and management of patients with osteoporotic fracture. *Osteoporos Int*. 2003;14(12):1028-1034. https://doi.org/10.1007/s00198-003-1507-z PMID:14600804
67. Domeij-Arverud E, Labruto F, Latifi A, Nilsson G, Edman G, Ackermann PW. Intermittent pneumatic compression reduces the risk of deep vein thrombosis during post-operative lower limb immobilisation: a prospective randomised trial of acute ruptures of the Achilles tendon. *Bone Joint J*. 2015;97-B(5):675-680. https://doi.org/10.1302/0301-620X.97B5.34581 PMID:25922463
68. Åkesson K, Marsh D, Mitchell PJ, et al; IOF Fracture Working Group. Capture the fracture: a best practice framework and global campaign to break the fragility fracture cycle. *Osteoporos Int*. 2013;24(8):2135-2152. https://doi.org/10.1007/s00198-013-2348-z PMID:23589162
69. Nakayama A, Major G, Holliday E, Attia J, Bogduk N. Evidence of effectiveness of a fracture liaison service to reduce the re-fracture rate. *Osteoporos Int*. 2016;27(3):873-879. https://doi.org/10.1007/s00198-015-3443-0 PMID:26650377
70. Gupta MJ, Shah S, Peterson S, Baim S. Rush Fracture Liaison Service for capturing "missed opportunities" to treat osteoporosis in patients with fragility fractures. *Osteoporos Int*. 2018;29(8):1861-1874. https://doi.org/10.1007/s00198-018-4559-9 PMID:29869038
71. Wu C-H, Chen CH, Chen PH, et al. Identifying characteristics of an effective fracture liaison service: systematic literature review. *Osteoporos Int*. 2018;29(5):1023-1047. https://doi.org/10.1007/s00198-017-4370-z PMID:29525971
72. Sarafrazi N, Wambogo EA, Shepherd JA. *Osteoporosis or Low Bone Mass in Older Adults: United States, 2017–2018. NCHS Data Brief, no 405*. National Center for Health Statistics; 2021. doi: https://dx.doi.org/10.15620/cdc:103477
73. Office of the Surgeon General (US). *Bone Health and Osteoporosis: A Report of the Surgeon General*. Office of the Surgeon General (US); 2004. PMID: 20945569

Table A. Secondary Causes of Osteoporosis[30-35]

| | |
|---|---|
| Osteomalacia | Vitamin D Deficiency |
| Malabsorption (Celiac Disease, Gastric Bypass) | Hypogonadism/Premature Ovarian Insufficiency |
| Primary Hyperparathyroidism | Hyperprolactinemia |
| Hypophosphatasia | Hyperthyroidism |
| GH Deficiency | Acromegaly |
| Chronic Kidney Disease | Cushing's Syndrome |
| Osteogenesis Imperfecta | Inflammatory Bowel Disease |
| Idiopathic Hypercalciuria/Kidney Stones | Primary Biliary Cirrhosis |
| Multiple Myeloma/MGUS | Systemic Mastocytosis |
| Beta Thalassemia Major | Transplant (solid organ, stem cell) |
| Rheumatoid Arthritis | Eating/Exercise Disorders and low BMI |
| Ankylosing Spondylitis | Systemic Lupus Erythematosus |
| Diabetes Mellitus (impaired bone microarchitecture) | COPD, Cystic fibrosis |
| Multiple Sclerosis | Immobility/Spinal Cord Injury |
| HIV | Hemochromatosis/Chronic Liver Disease |
| Ehlers-Danlos Syndrome | Marfan Syndrome |
| Alcoholism | Renal Tubular Acidosis |
| Medications (glucocorticoids, excess thyroid hormone, anti-epileptic drugs, aromatase inhibitors, depot medroxyprogesterone, etc) | |

Table B. Suggested Lab Evaluation for Secondary Causes of Osteoporosis[30-32,36]

| |
|---|
| Complete Blood Count (CBC) |
| Comprehensive Metabolic Panel (CMP) |
| Serum 25-hydroxyvitamin D (25OHD) |
| Serum phosphorous |
| 24-hour urine calcium, creatinine and sodium |
| Parathyroid Hormone (PTH) - particularly if abnormal serum calcium |
| Testosterone (in men) |
| TSH (if on thyroid hormone replacement) |

Table C. NOF Guidelines Criteria for Performing Dedicated Vertebral Imaging[31]

| |
|---|
| Women and men ≥50 years old with a low trauma fracture, subjective (historical) height loss of ≥1.5 inches (4 cm), prospective height loss of ≥0.8 inches (2 cm), or glucocorticoid exposure. |
| Women 65-69 years old and men 70-79 years old with a T-score ≤ -1.5 |
| Women ≥70 years old and men ≥80 years old with T-scores ≤ -1.0 |

Table D. Individuals in Whom Pharmacological Therapy Should Be Considered[30,31,37,38]

| |
|---|
| Postmenopausal women and men > 50 years old meeting WHO BMD Criteria from DXA (T-score ≤-2.5 at the lumbar spine, femoral neck, total femur, or (in certain circumstances) 33% radius) |
| Fragility Fracture |
| Postmenopausal women and men > 50 years old with osteopenia at Increased Risk of Fracture as determined by fracture risk calculator, such as FRAX |
| Rapid, non-physiologic bone loss (e.g., glucocorticoids, aromatase inhibitors, etc) |

Table E. Pharmacological Treatment Options for Osteoporosis

| Medication | Dose/Frequency | Fracture Risk Reduction (in post-menopausal osteoporosis) | Comments |
|---|---|---|---|
| Bisphosphonates | | | |
| Alendronate [48-51] | 70 mg PO weekly | 35-65% Vertebral<br>23% Non-vertebral<br>45-55% Hip | Can cause hypocalcemia and esophagitis. |
| Risedronate [52, 53] | 35 mg PO weekly | 41% Vertebral<br>39% Non-vertebral<br>30% Hip | Can cause hypocalcemia and esophagitis. |
| Ibandronate [54] | 150 mg PO monthly | 62% Vertebral | Can cause hypocalemia and esophagitis.<br>No evidence of hip fracture protection |
| Zoledronate [55] | 5 mg IV annually | 70% Vertebral<br>25% Non-vertebral<br>41% Hip | Can cause hypocalcemia<br>~32% have an acute phase reaction with their first infusion consisting of fever, myalgias, and flu-like symptoms lasting 24-72 hours [55] |
| Raloxifene [56] | 60 mg PO daily | 30% Vertebral | No data for hip fracture prevention |
| Denosumab [57] | 60 mg subcutaneously every 6 months | 68% Vertebral<br>20% Non-vertebral<br>40% Hip | Can cause hypocalcemia and musculoskeletal pain<br>Cannot be stopped/delayed due to increased risk of multiple rebound vertebral compression fractures [58] |
| Teriparatide [59] | 20 mcg subcutaneously daily x 2 years | 65% Vertebral<br>40% Non-vertebral | Contraindicated if history of radiation<br>Must be followed by anti-resorptive therapy to avoid loss of BMD gains |
| Abaloparatide [60] | 80 mcg subcutaneously daily x 2 years | 86% Vertebral<br>43% Non-vertebral | Contraindicated if history of radiation<br>Must be followed by anti-resorptive therapy to avoid loss of BMD gains |

| | | | |
|---|---|---|---|
| | | | Not FDA-approved in men<br>Unlike teriparatide, does not need to be refrigerated |
| Romosozumab [47] | 210 mg subcutaneously monthly x 12 months | 73% Vertebral | May increase risk of myocardial infarction, stroke and cardiovascular death<br>Not FDA-approved in men |

*Calcitonin is no longer commonly used for osteoporosis